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Hypoglycaemia due to Autoimmunity

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ABSTRACT

Hirata disease is an insulin autoimmune disease characterized by non-exogenous hyper insulinemic postprandial hypoglycemia due to elevated insulin autoimmune antibodies (IAS), with no exogenous insulin and no pathological abnormalities of pancreatic islets cells, the diagnosis is often missed due to the rarity of the disease, failure to diagnose Hirata disease in a timely manner often results in exposing the patients to unnecessary investigation and surgical procedures.

Disease is uncommon in non -Asian population, among Caucasian population, most of the cases is due to drug exposure, autoimmune diseases or hematological malignancies, sometimes Hirata disease can be triggered by viral infection.

In this manuscerpit we will present a case of autoimmune insulin hypoglycemia, patient was subjected to few unnecessary investigations before reaching the correct diagnosis, we reviewed the recent literatures about autoimmunity of endogenous insulin hypoglycemia, we also will suggest the best practice based on our experience given that there is no guidelines to follow due to the rarity of the disease.

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Case Report

37 single lady from New Zealand referred by her GP to endocrinologist because of recently discovered symptomatic hyperthyroidism, where T4 and T3 were elevated, TSH was nearly undectable, ultrasound of the neck confirmed diffuse homogenous hypodensity, of the thyroid gland with no retrosternal extension, nuclear scan confirmed uniform uptake of isotope consistent with graves' disease.

Antibodies testing showed high Anti-Thyroperoxidase antibodies at 1500 iu/ml (less than 9 iu/ml) TSH receptor antibody was elevated at 130iu/l (1.75iu/l), thyroglobulin antibody (TgAB) 500iu/ml (less than 100 iu/ml), Thyroid stimulating immunoglobulin antibody (TSI) 700%(less than 130%).

Hyperthyroidism was confirmed to be due to graves' disease, reexamining the patient revealed early clubbing and pretibial myxedema with no eye signs, patient opted to start on medication and declined radioactive iodine, patient was prescribed Methimazole (Tapazole) 30 mg daily and follow-up with repeat thyroid testing in 8 weeks, Patient improved clinically, repeated thyroid function showed chemical and serological improvement, Methimazole tapered to 15 mg daily, patient discharged back to GP for follow up and follow up with specialist in one year time.

Three months later patient experienced a syncopal episode lasted for 10 minutes when she had severe dizziness, sweating and confusion, ambulance was called, blood sugar was 3.5 mmol/L at that time, other vital signs showed blood pressure 130/60, no fever, heart rate 120/min regular, ECG did not show any arrythmia, patient recovered back to normal after given 50ml, 20% dextrose.

On arrival to hospital, patient was Asymptomatic with normal vital signs, metabolic panel which included blood sugar, calcium, phosphate, Mg, were all normal, Troponin I and high sensitive troponin were negative, D dimer was negative for her age, CT head was unremarkable, Patient denied taking any medication whether prescribed or from over the counter, CXR was normal, septic screen was ordered.

Patient offered to stay overnight in the hospital but she preferred to go home. Two days later patient started to have shaking for one minute and lost consciousness, ambulance was called, Blood sugar found to be 2.5mmol/L, 100 ml 10% dextrose infusion was administered.

On arrival to Hospital, patient was almost back to normal, physical examination in ED showed normal vital signs, neurological examination did not show any neurologic deficit, examination of the heart, lung and abdomen were absolutely normal, ECG was sinus with no ST-T changes, urgent CT Head did not show any acute pathology, patient admitted to medical department for more investigation and observation.

The following investigations were performed, CXR, X ray abdomen, Full blood count, inflammatory markers, fasting Blood sugar pre-prandial and postprandial blood sugar with breakfast, lunch and dinner, Liver Function tests, metabolic panel, troponin,

early morning ACTH and cortisone, Cynacthen test, Thyroid function test.

All above mentioned tests and images were either negative or normal, patient was reassured and discharged home. Two weeks later, patient was invited for a lunch, immediately after taken her food, she started to feel sick and nauseated with sweating and palpitation, and she lost consciousness, ambulance service was called, her pulse wea 120/min regular, her blood sugar was 2.6 mmol/L, 50 ml 20% dextrose was administered, when arrived to the hospital, patient was conscious, orinted in time, place and person, blood sugar was 10mmol/L ECG, CXR, Urgent CT Head, metabolic panel was normal, patient was admitted to the hospital.

For further investigation, CT neck, chest, abdomen and pelvis were performed, serum lipase, amylase, fecal elastase, celiac screen, autoimmune screen which included AND, DNA, ACCP, anticentromere antibodies, Anti SCL70, Anti LA, Anti RO, Anti Sm, Anti Jo1, Anti U1RNP, CK, serum lactate, ammonia, Septic screen, virology screen, long chain fatty acids, tumor markers muscle biopsy to exclude mitochondrial disease, all blood testing came either normal or negative, CT whole body did not show any evidence of malignancy, initial result of muscle biopsy before immune staining was normal.

Patient was reassured again and discharged home. Patient admitted next day with seizure and hypoglycemia which was aborted with IV dextrose. Neurology and endocrinal service were asked to see the patient and advise about further investigation and management, neurologist advised for CSF study, EEG and MRI brain, which was performed same day and did not show any abnormality, endocrinology advised for CT-PET scan, and MIBG scan.

All investigation performed next day and did not show any abnormalities, patient reassured and advised for discharge home, patient developed another seizure just before discharge, blood sugar was 3mmol/L. Blood was saved for proinsulin, insulin, C peptide, 100ml of 10% dextrose was infused with complete recovery, the result of blood testing during hypoglycemia confirmed high C -peptide and insulin.

Patient was reviewed by endocrinologist who advised for endoscopic abdominal ultrasound which failed to show any insulinoma, this was followed by selective arterial calcium stimulation to localize insulinoma. Which failed to localize any insulinomas or nesidioblastosis.

Given the recurring hypoglycemia, patient was offered intraoperative localization of insulinoma, Patient asked for a second opinion before considering surgery, appointment was arranged to be seen by endocrinal scientist, another endocrinologist and a pancreatic biliary surgeon. Patient admitted in another endocrinology center, patient blood was saved for blood sugar, serum insulin, serum proinsulin, and C-peptide over 72 hours fasting, when blood sugar dropped to 2.5 mmol/L, serum insulin and C-peptide was highly elevated, the ratio of Insulin to C-peptide was 1.2.

Blood was saved for insulin autoimmune antibodies (IAA), thyroid antibodies including TSH receptor antibodies, autoimmune screen, adrenal antibodies, viral study, protein and serum electrophoresis, light chain assay, flowcytometry. Blood results were very significant for a very high titer for insulin autoimmune antibodies and this was confirmed by Gel filtration chromatography which detected macroinsulin.

Diagnosis was confirmed as insulin autoimmune syndrome (IAS), most probably due to methimazole, Patient was counselled about the diagnosis of Insulin Autoimmune syndrome, and offered to stop Methimazole and choose between surgery or radioactive iodine for treatment of gravs disease. Patient opted for radioactive iodine, patient advised to start on frequent small size meal with low hydrocarbonate portion, patient continued to have regular visit to endocrinology clinic with regular surveillance of autoimmune insulin antibodies titer which was almost undectable after three months with no further hypoglycemia, patient considered cured and discharged back to GP.

Discussion

Autoimmune insulin hypoglycemia is characterized by hypoglycemia in the presence of elevated insulin, Proinsulin and C-Peptide and antiinsulin antibodies or antiinsulin receptor antibodies. Although it is very uncommon in non -Asian population, it is the third leading cause of hypoglycemia in Japan, making the correct diagnosis early will save the patient few expensive unnecessary blood and imaging testing in addition to hospital admissions and few outpatients clinic visiting's, Hypoglycemia could be postprandial, fasting or both. Obtaing a detailed through clinical history is fundamental to choose the appropriate investigations, specially in elderly patients with Diabetes and chronic renal failure.

In Patients with diabetes, overtreatment with insulin and long-acting sulphonyl urea should be ruled out before starting investigation for uncommon causes, post- bariateric surgery is not uncommon cause of postprandial hypoglycemia specially in Roux-en-Y gastric by Pass surgery (RYGB), usually postprandial due to early Dumping syndrome, reducing the size and the carbohydrate portion can cure hypoglycemia, also few cases of hypoglycemia had been reported after sleeve gastrectomy.

In addition to diatry modification, patient can be treated with Acarbose and somatostatin analogues, Other common causes of hypoglycemia includes malnutrition, sepsis, liver cirrhosis, adrenal insufficiency, malignancy. Although autoimmune insulin hypoglycemia is rare, it should be considered in the differential diagnosis even among coccasions to avoid over investigations for insulinoma, hypopituitarism. Insulin Autoimmune syndrome was originally described in 1970 by Yukimasa Hirata and colleagues (in Japan) in a 47-year-old obsess man with recurrent hypoglycemia, disease is named (Hirata disease).

Hirata disease is not common among non-Asian patients, but few cases reported recently among caucasian, Insulin autoimmune syndrome or Hirata disease is characterized by recurrent postprandial, fasting or both postprandial and fasting hypoglycemia where patient will develop Whipple's traid in the presence of high insulin, proinsulin and C-peptide, it is fundamental that patient is not exposed to exogenous insulin or long-acting sulphonyl urea, and patient has normal structural pancreatic islets, also patients have high titer of insulin antibodies, ratio between insulin to C-peptide is more than 1 in contrast with insulinoma where C-peptide to insulin ratio is more than 1, the pathogenesis of hypoglycemia in Hirata syndrome insulin antibodies bind insulin molecule to form a macromolecule of insulin–insulin autoimmune antibodies complex that cause fluctuation of serum glucose through a double-phase mechanism, the initial phase causing hyperglycemia due to prevention of insulin to bind to insulin receptor by insulin antibodies ,this will follow by erratic release of insulin from the insulin antibodies complex regardless of the blood sugar level at that time causing hypoglycemia, the trigger

of insulin antibodies are few which includes viral infection like measles, mumps, rubella, varicella zoster, hepatitis C, coxsackie virus, and medications like methimazole, propylthiouracil, carbimazole, glutathione, methionine, Diltiazem, Captopril, Proconamide, steroids, penicillin G, interferon, monoclonal gammopathy of undetermined significance and multiple myeloma had been reported as a triggers for autoimmune hyperinsulinemia hypoglycemia.

although insulin autoimmune hypoglycemia is induced by antithyroid medication, the role of graves' disease is not confirmed, medications containing sulfhydryl groups are associated with insulin autoimmune hypoglycaemia, probably the sulfhydryl component is able to bind and reduce Insulin chain A and B Causing the insulin to be immunogenic, although Autoimmune insulin hypoglycemia is very common among Chinese and Japanese population, it is very uncommon among Caucasian, this variance was explained by genetic predisposition and strong association with human leucocyte antigen (HLA)DR4, DRB1 0406 and DRB1 0403 which is common among Japanese and Chinese population, Caucasian patients mainly express HLA-DR4 in autoimmune insulin hypoglycemia.

It is of note that exogenous insulin can induce insulin antibodies complex, it is usually weak and tend to disappear when insulin stopped or changed to another form of insulin, it is worth mentioning although the definition of autoimmune insulin hypoglycemia that patient is not exposed to exogenous insulin , some diabetic patients might developed autoimmune insulin hypoglycemia, Insulin autoimmune syndrome is classified as type V11 hypersensitivity caused by autoantibodies against circulating target protein or hormones, Hirata Disease can occur in patients with established autoimmunity and in patients with type 1 DM who got the disease at a younger age.

In normal person when blood glucose drops to below 3mmol/L, insulin will be suppressed to below 18mmom/L and C-peptide below 0.2nmol/l, if proinsulin and C-peptide are elevated or inappororiatry normal, Exogenous insulin, Sulphonyl urea and Insulinoma should be ruled out, exogenous insulin should be suspected if insulin is elevated but proinsulin and C-peptide are low.

In patient with insulin autoimmune hypoglycemia, the insulin antibodies complex caused prolongation of the half-life of insulin from 5 minutes to few hours, while the half-life of C-peptide remains unaffected (25-35 minutes), this leads to increase the insulin level but not the C-peptide which leads to insulin/C-peptide ratio more than 1, patients with insulinoma will have C-peptide / Insulin ratio more than one due to the shorter half-life of insulin (5-10 Minutes).

Few cases reported in the literatures where antibodies bind firmly to both insulin and C-peptide delaying the half-life of both and making the diagnosis extremely difficult. Most of the patients will have a self-limiting disease and disease usually recover after withdrawing the trigger agent, small meals with low carbohydrates can induce remission.

Some patients will need pharmacological treatment, alpha-glucosidase inhibitor (Acarbose) can treat postprandial hypoglycemia as it delays carbohydrate absorption, generally it is poorly tolerated by patients because of the gut Sid effect like diarrhea and flatus.

In patients with high titer of antibodies and difficult to control disease, plasmapheresis and steroids are other options, Rituximab had been used with success specially in patients with insulin autoimmune hypoglycemia in patients with type 1 DM with exogenous insulin. Patients with monoclonal gammopathy of undermined significance and multiple myeloma will need chemotherapy to induce remission of insulin autoimmune hypoglycemia.

Insulin Resistance Syndrome Type B

This is a genetically predisposed syndrome which comprise few syndromes, characterized by insulin resistance and increased B-cell insulin secretion, usually patient develop disease at a younger age. Patients usually develop autoantibodies to cell surface receptor, other autoimmune markers included TSH receptor antibodies, Acetylcholine receptor antibodies, or gonadotrophin receptor antibodies causing graves' disease, myasthenia gravis and ovarian failure respectively, patient usually develop severe form of insulin resistance, some patients will have underlying autoimmune Ruhmatological diseases like Systemic lupus erthrotomies mixed connective tissue disease, or jargon syndrome.

Phenotypic manifestation of severe insulin resistance could be a paraneoplastic manifestation of underling hematological malignancy like lymphoma and myeloma malignancy, patients can develop severe refractory hyperglycemia, and hypoglycemia. Common manifestations are acanthosis nigricans, lipodystrophy, hirsutism, polycystic ovarian disease Insulin resistance, hyperandrogenism, obesity, anovulatory cycles, treatment included control of hyperglycemia, remove triggers and immunomodulation including steroids and plasmapheresis, rutixmab, and Cyclophosphamide [1-25].

Conclusion

Autoimmune insulin hypoglycemia and insulin resistance type B syndrome are rare causes of hyper insulinemic hypoglycemia, but they continued to be reported in multiple literatures, immunoassay of insulin, proinsulin, C-Peptide and insulin immune antibodies are very valuable tool to rule out the syndrome and save patients expensive investigations and unnecessary surgical operations.

Autoimmune insulin syndrome and insulin syndrome type B should be in the differential diagnosis of hyperinsulinemia hypoglycemia, and should be ruled out before proceeding for any expensive investigations or surgery.

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